UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

23565 7590 02/27/2003

KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/27/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/804,584	Alberts et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above, claim(s) *3, 5-14, 20, and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 15-19, 21, and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election of the species from I: a method wherein inhibition or elimination of effective T-cell help is attained by inhibiting signaling consequent to dendritic cell-t cell engagement and the species from II: viral antigens.

2. Claims 1-41 are pending. Claims 23-41, drawn to non-elected inventions are withdrawn from consideration. Claims 3, 5-14 and 20, drawn to non-elected species, are also withdrawn from consideration. Claims 1, 2, 4, 16-19, 21 and 22 are examined on the merits.

Specification

3. The disclosure is objected to because of the following informalities: The application claims priority to 09/545,958 rather than 09/565,958.

Appropriate correction is required.

Oath/Declaration

4. The Declaration is defective for not claiming priority to applications 09/565,958 and 09/251,896.

Claim Rejections - 35 USC § 112

5.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 4, 16-19, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A)Claim 1 is vague and indefinite in the recitation of "pre-selected antigen". It is unclear how a "pre-selected antigen" differs from an antigen, and the specification provides no definition

of pre-selected antigen that would limit the metes and bounds of the claims with respect to the antigens encompassed therein. For purpose of examination, the claim will be read as encompassing "an antigen" rather than "a pre-selected antigen".

(B)Claim 17 is rendered vague and indefinite by reference to FK506 which is a trade name.

(C)The recitation of "a cellular portion" in claim 1 is vague and indefinite in that it is not clear if applicant intends that a fractionation of the dendritic cells or dendritic cells and T-cells would take place to result in a cellular portion, or if applicant intends that the dendritic cells per se, rather than the supernatant or culture medium, constitute the "cellular portion". For purpose of examination, the later condition will be considered.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 4, 15, 16, 17, 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) in view of Migita et al (Journal of Clinical Investigation, 1995, Vol. 96, pp. 727-732) and Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) and Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-4609) .

Claim 1 is drawn to a method for inducing tolerance in a mammal to an antigen comprising the steps of isolating peripheral blood mononuclear cells from said mammal; isolating dendritic cells from said peripheral blood mononuclear cells; exposing said dendritic cells ex vivo to apoptotic cells expressing said antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+T cell help; introducing a cellular portion of step (c) into said mammal; wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen. Claim 4 embodies the method if claim 1 wherein said absence of effective CD4+ T-cell help is achieved by including in step (c) at least one agent that inhibits or eliminates effective CD4+ T cell help. Claim 15 embodies the method of claim 4 wherein said agent inhibits signaling consequent to dendritic-cell CD4 T cell engagement. Claim 16 embodies the method of claim 15 wherein said agent is a FKBP antagonist. Claim 17 specifies that the FKBP antagonist is FK506. Claim 19 embodies the method of claim 1 wherein said antigen is a viral antigen. Claim 21 embodies the method of claim 1 wherein the infusion of the cellular portion of step (c) is done after a period of time. Claim 22 embodies the method of claim 1 wherein said mammal is human.

Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) teach that apoptotic cells are phagocytosed by dendritic cells. Rovere et al teach that dendritic cells control there own maturation by selectively releasing maturation factors when challenged with a relative excess of dendritic cells. (Page 4470, first column, lines 5-8). Rovere et al point out that dendritic cells secrete substantial amounts of TNF-alpha when challenged with high numbers of apoptotic cells(page 4469, second column, lines 5-7 of the first full paràgraph).

Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) teach that dendritic cells are involved in the induction of peripheral tolerance versus central tolerance (page 250, first column, third paragraph under the heading "Dendritic cells and T-cell tolerance").

Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732) teach that FK506 exclusively induced apoptosis of antigen-stimulated T-cells (page 731, first column, lines 11-16 of the first full paragraph, and second column, first paragraph).

Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-4609) teach that FK506 in combination with CTLA4Ig abrogated the immune response against adenovirus proteins. Guibinga et al teach that CD+8 lymphocytes which destroy adenovirus infected cells counter the beneficial effects of adenovirus mediated gene therapy, and that the elimination of the immune response against the adenovirus was necessary in the treatment of genetic diseases which would require long-term transgene expression and repeated vector delivery.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to induce tolerance to the adenovirus by means of contacting peripheral blood dendritic cell with apoptotic cells which have been infected with the adenovirus; growing the dendritic cells until they mature; administering said mature dendritic cells to a human in need of adenovirus mediated gene therapy in addition to FK-506 and CTLA4Ig, wherein CD+8 cells which are activated by said dendritic cells will undergo apoptosis resulting in tolerance to said adenovirus antigens. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rovere et al on the cross presentation of antigens by means of phagocytosis of apoptotic cells by dendritic cells; the teaching of Banchereau et al on the mediation of peripheral tolerance by dendritic cells; the teachings of Migita et al on the specific induction of apoptosis by FK506 in activated versus resting T cells and the teachings of Guibinga et al on the abrogation of the CTL immune response against adenovirus antigen by the administration of FK506 and CTLA4Ig to mice. Further the administration of FK506 would inherently comprise the claimed properties of being a FKBP

antagonist, and inhibiting or eliminating effective T-cell help consequent to dendritic-cell CD4 T-cell engagement.

9. Claims 1, 4, 15-19, 21 and 22 rejected under 35 U.S.C. 103(a) as being unpatentable over Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) and Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732) and Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) and Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-4609) as applied to claims 1, 4, 15, 16, 17, 19, 21 and 22 above, and further in view of Li et al (Transplantation, 1998, Vol. 66, pp. 1387-1388) and Sehgal (Clinical biochemistry, 1998, Vol. 31, pp. 335-340). The embodiments of claims 1, 4, 15-19 21 and 22 are set forth above. Claim 18 embodies the method of claim 16 wherein said TOR antagonist is rapamycin. The combination of Rovere et al and Migita et al and Banchereau et al and Guibinga et al render obvious claims 1, 4, 15, 16, 17, 19, 21 and 22 for the reasons set forth above. Neither of the aforesaid references teach rapamycin for the inhibition or elimination of effective CD4+ T cell help consequent to dendritic cell-CD4 T cell engagement or by means of a TOR antagonist.

Li et al teach that CTLA4Ig combined with rapamycin results in a permanent tolerization to a tissue engraftment. Li et al teach that rapamycin blocks Il-2 induced proliferative but not apoptotic signals is required to achieve tolerance to an antigen (page 1387, second column, second full paragraph). Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which block the Il-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S-phase in T-cells (page 336, second column, lines 4-9).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute rapamycin for FK506 in the method of inducing tolerance in an animal as rendered obvious by the combination of references above.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Li et al on the efficacy of using rapamycin in the combined stimulation blockade to produce tolerance and the teachings of Sehgal on the rapamycin:FKBP complex as an inhibitor of TOR. One of skill in the art would recognize that rapamycin could be substituted for FK506 in the combined costimulation blockade taught by Guibinga et al.

10. All claims are rejected.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

February 23, 2003